REMARKS

Claims 23-37 were pending in this case. Claims 1-22 were previously cancelled. With this reply claims 24 and 26 have been cancelled. Thus, with this reply claims 23, 25, and 27-37 are pending and under examination. Claims 23, 24, 26, and 28-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and lack of adequate written description. Claims 23, 24, 26, and 28-33 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Claims 23-33 stand rejected under 35 U.S.C. § 103, for obviousness. Each of these rejections is addressed below.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 23, 24, 26, and 28-33 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. As a basis for rejection, the Office asserts that, while the specification is enabling for the treatment of asthma and arterial hypertension, the method claims lack enablement with respect to treating every known and yet unknown disease conditions associated with constriction of smooth muscle cells. In particular, the Office Action at page 2 states:

> ...the examiner does not agree with the applicants arguments that the specification is enabling for treating every known and yet unknown disease conditions associated with constriction of smooth muscle cells. There is no teaching or suggestion present in the instant specification regarding any other disease condition associated with the constriction of smooth muscle cells besides asthma and arterial hypertension.

Applicants have addressed this rejection by amendment of the claims.

With this reply claim 23, and dependent claims 28-33, are now limited to the treatment of arterial hypertension and asthma. Claims 24 and 26 have been cancelled.

In view of the amendment to the claims, applicants request that the rejections for lack of enablement be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 23, 24, 26, and 28-33 stand rejected under 35 U.S.C. § 112, first paragraph,

for lack of adequate written description. As a basis for rejection, the Office asserts that, while the specification provides a written description for the treatment of asthma and arterial hypertension, there is no written description of any other disease condition or pathologies which are linked to constriction of smooth muscle cells. In particular, the Office Action at page 3 states:

> The instant specification mentions only arterial hypertension and asthma as the disorders or pathologies which are linked to smooth muscle cell constriction (see page 2, lines 10-15). However, there is no written description of any other disease condition or pathologies which are linked to constriction of smooth muscle cells.

Applicants have addressed this rejection by amendment of the claims.

With this reply claim 23, and dependent claims 28-33, are now limited to the treatment of arterial hypertension and asthma. Claims 24 and 26 have been cancelled.

In view of the amendment to the claims, applicants request that the rejection for lack of written description be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 23, 24, 26, and 28-33 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness, on the basis that the specific pathologies and conditions that are associated with the constriction of smooth muscle cells are not defined. The claims as amended now specify specific pathologies (i.e., asthma and arterial hypertension), so this rejection can therefore be withdrawn.

Rejection under 35 U.S.C. § 103

Claims 23-33 stand rejected under 35 U.S.C. § 103(a) as obvious over Becq (U.S. Patent 6,630,482; hereinafter "Becq"). As a basis for this rejection the Office Action at page 4 states:

> Becq discloses benzoquinolizinium compounds (see columns 11-13) for treating obstructions of bronchial routes and cardiovascular diseases (see column 4, lines 12-15). Becq meets all the limitations of instant claims except that it does not mention treating pathology associated with the constriction of smooth muscle cells. However, disease

> conditions such as asthma and arterial hypertension are encompassed by the terms --- obstructions of bronchial routes and cardiovascular diseases, respectively. Therefore, it would have been obvious to one skilled in the art to treat asthma and arterial hypertension with reasonable expectation of success since Becq teaches utility of benzoquinolizinium compounds for treating obstructions of bronchial routes and cardiovascular diseases.

Applicants respectfully disagree and address this rejection with the following remarks.

Becq teaches the use of some benzo[c]quinolizinium compounds as activators of the cystic fibrosis transmembrane conductance regulator (i.e., "CFTR") channel. Becq suggests that the benzo[c]quinolizinium compounds can be used to treat certain specific conditions associated with a pathological dysregulation of ion flow at the CFTR receptor of epithelial cells, including conditions such as cystic fibrosis. Most importantly, nowhere in Becq is it taught or suggested that benzo[c]quinolizinium compounds can be used to treat conditions arising from the constriction of smooth muscle cells, such as asthma or arterial hypertension, as required by the pending claims. Thus, Becq describes the treatment of an entirely different patient population (patients with disorders in transmembrane ion flow at epithelial cells) than the patient population specified in the pending claims (patients suffering from the constriction of smooth muscle cells). These different patient populations suffer from distinct medical conditions (e.g., cystic fibrosis versus asthma or arterial hypertension), characterized by different underlying pathophysiologies (e.g., dysfunctional secretion versus constriction), and characterized by dysfunction at different cell types (i.e., epithelial cells versus smooth muscle cells). The differences between Becq and the pending claims are described in more detail below.

Becq teaches the treatment of patients suffering from disorders in transmembrane ion flow at epithelial cells.

The CFTR channel is a chloride channel involved in cystic fibrosis (also known as mucoviscidosis), as well as numerous other pathologies associated with the physiology of

epithelial cells. In an epithelial cell, transportation of water and electrolytes is associated with an increase in the permeability of the cell membrane to the ions K^+, Na^+, and Cl^-. These movements are linked to the activity of ion channels, which are specialized proteins integrated into the membrane allowing passive diffusion of ions. The techniques of molecular electrophysiology (i.e., patch clamping) allow recording at the unit level of the openings and closings of an ion channel and make it possible to study transepithelial ion transport, regulation, and pathological dysregulation (see Becq at column 1, lines 1 to 25).

In the case of cystic fibrosis, mutations of the CFTR gene alter the function of the CFTR channel. As a result, the transportation of electrolytes becomes abnormal, which leads to particular pathological conditions arising from defective secretion linked to the poor functioning of the CFTR channels (see Becq at column 1, lines 39-49).

Becq describes patch-clamp studies showing that benzo[c]quinolizinium compounds stimulate the opening of the CFTR channel by a route independent of cAMP or intracellular calcium, thus representing a new family of CFTR channel activators. These results are obtained using epithelial cells of the respiratory tract which secrete mucus. In patients with cystic fibrosis, this mucus is very thick due to the lack of water, compromising the evacuation of bacteria from the lung and leading to an inflammation of the pulmonary alveoli (see Becq at Example IV, column 27, line 59, to column 34, line 35). Becq does not teach or suggest performing similar studies on human non-epithelial cell lines, such as smooth muscle cells.

Becq specifically teaches the treatment of pathologies associated with disorders in transmembrane ion flow in the epithelial cells of a subject (see Becq at column 4, lines 3-5). All of the specific conditions recited by Becq, such as cystic fibrosis, are conditions arising from defective transmembrane ion flow, which is inhibited by poor functioning of the CFTR channels. In the case of cystic fibrosis, this results in dysfunctional mucus secretion and compromised lung function.

As noted above and by the Office in making this rejection, nowhere in Becq is it taught or suggested that benzo[c]quinolizinium compounds can be used to treat a condition characterized by the constriction of smooth muscle cells, such as asthma or arterial hypertension. Furthermore, nowhere in Becq is it taught or suggested that benzo[c]quinolizinium compounds can be used to treat a condition that is not a disorder of transmembrane ion flow at epithelial cells.

Pending claims 23-33 are directed to the treatment of patients suffering from constriction of smooth muscle.

The present invention is based on the inventor's discovery that benzo[c]quinolizinium compounds are able to antagonize the constriction of smooth muscle, such as aorta rings or tracheal rings, and therefore are useful for the treatment of conditions associated with the constriction of smooth muscle, such as asthma and arterial hypertension. This discovery is related to the inventor's identification of CFTR expression in smooth muscle cells, and characterization of the effects of CFTR activity in these cells. This activity is different from CFTR channel activation in epithelial cells as it involves either an action on the depolarization of the smooth muscle cells (in case of the results obtained on constrictions due to KCl) or interaction with the alpha-1 adrenergic receptor (in case of the results obtained on constrictions due to arterenol). The cells of the smooth muscle are completely different from the epithelial cells used in the assays of Becq.

Asthma and arterial hypertension are conditions in which passageways (i.e., airways and blood vessels) are reversibly narrowed as a result of the constriction of smooth muscle cells. These conditions are unlike those described by Becq in that neither of these conditions is associated with disrupted transmembrane ion flow at epithelial cells.

The disorders in transmembrane ion flow at epithelial cells taught by Becq do not encompass the conditions associated with the constriction of smooth muscle recited by the pending claims

As a basis for this rejection the Office relies solely upon the fact that asthma and arterial hypertension are encompassed by the generic terms "obstructions of bronchial routes" and "cardiovascular diseases" recited by Becq. Applicants respectfully disagree.

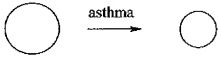
With respect to the conditions that can be treated with , Becq at column 4, lines 3-15, recites:

> In this respect, the object of the present invention is to provide new medicaments for treatment of pathologies associated with disorders in transmembrane ion flow, in particular of chlorine, in the epithelial cells of a human or animal organism.
>
> The object of the present invention is more particularly to provide new medicaments which can be used in the context of treatment of cystic fibrosis, of prevention of rejection of cytotoxic drugs (in particular antitumoral drugs), or of prevention or treatment of obstructions of bronchial routes or of digestive tracts (in particular pancreatic or intestinal), or also in the context of treatment of cardiovascular diseases.

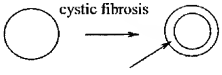
In view of the conditions recited in Becq and the experiments described in Becq, one of skill in the art would conclude that Becq teaches only the use of benzo[c]quinolizinium compounds for the treatment of disorders associated with disrupted transmembrane ion flow at epithelial cells, and not the treatment of any and all bronchial obstructions and cardiovascular diseases.

In contrast to the teachings of Becq, the present claims are directed to the treatment of conditions characterized by the constriction of smooth muscle, such as asthma or arterial hypertension, not disrupted transmembrane ion flow at epithelial cells.

For example, in contrast to asthma, cystic fibrosis is a heritable genetic disorder of the secretory glands, including glands that make mucus and sweat, that results in a clogging of the airways in the lungs due to mucosa build-up. The difference between asthma and cystic fibrosis is shown in Figure 1, below.



constriction of the smooth muscle



mucus layer

Figure 1

Thus, in asthma muscle constriction leads to a narrowing of the bronchi whereas in cystic fibrosis the obstruction is due to a build-up of secreted mucus in the bronchi.

The patient populations taught by Becq
are, by themselves, insufficient
to render the pending claims obvious.

Applicants submit that in view of the differences that exist between the patient populations taught by Becq and those presently claimed, no *prima facie* case for the obviousness of the pending claims has been established.

To establish a *prima facie* case for the obviousness of the pending claims the Office must identify a motivation to modify the prior art to arrive at the claimed methods for treating asthma and arterial hypertension. The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success. MPEP 2143.02.

As noted above and acknowledged by the Office, Becq teaches the treatment of

patients with disorders in transmembrane ion flow at epithelial cells, not patients suffering from the constriction of smooth muscle cells. These different patient populations suffer from distinct medical conditions (e.g., cystic fibrosis versus asthma), characterized by different underlying pathophysiologies (e.g., dysfunctional secretion versus constriction), and characterized by dysfunction at different cell types (i.e., epithelial cells versus smooth muscle cells).

In view of these differences, applicants submit that the requisite reasonable expectation of success is missing. There is no reason to expect, on the basis of Becq, that these same benzo[c]quinolizinium compounds could be effective for the treatment of conditions arising from the constriction of the smooth muscle, such as asthma or arterial hypertension.

In view of the remarks above, applicants request that the rejection for obviousness be withdrawn.

Support for Amendments to the Claims

Claims 23 has been amended to recite a condition selected from arterial hypertension and asthma. Support for the treatment of hypertension and asthma is found in the specification at page 2, lines 10-15.

Claims 25 and 27 have been amended to depend from claim 23.

No new matter has been added with these amendments.

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for one month, to and including September 4, 2009, and a check in payment of the required extension fee.

To expedite prosecution applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: September 2 2009

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